REMARKS

In the Office Action mailed October 17, 2007 the Examiner rejoined claims 61-63 with the claims of Group 1 as elected (with traverse) by Applicants on September 17, 2007. In order to advance business interests and without acquiescing to any argument raised by the Examiner while expressly reserving the right to prosecute the claims as filed, or claims similar thereto, in a subsequently filed patent application(s) Applicants have amended claims 3, 7, 11, 13, 14 and 47, withdrawn claims 9, 12 and 61-63 and added new claim 64. Claims 3, 7-11, 13-16, 47-5 and 64 are currently pending and under examination. All amendments to the claims find support in the application as filed.

The specification and Figures have been amended to correct inadvertent typographical errors and to provide sequence identifiers for nucleotide sequences in excess of nine bases that were not accompanied by a sequence identifier as originally filed. No new matter has been added by these amendments.

The Examiner, in the Office Action mailed October 17, 2007, rejected claims 3, 7-16, 47-51 and 61-63 and raised other objections to the pending application. Specifically, the Examiner made the following objections and rejections:

1. The Examiner objected to the use of acronyms in the claims.
2. The Examiner objected to informalities in the specification.
3. The Examiner alleged Applicants have introduced new matter.
4. The Examiner alleged Applicants are not compliant with sequence rules.
5. Claims 7, 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.
6. Claims 3, 7-16, 48-51, 61 and 62 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 6,229,002 to Janjic *et al.*
7. Claims 3, 7-10, 13, 48 and 61-63 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.*
8. Claims 3, 9, 10 and 47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0265912 to

Amendments to the Drawings:

Please replace Figure 17B and Figure 20 as originally filed with the enclosed replacement sheets (2 pages) of amended drawings. These sheets replace the original sheets including Figures 17B and 20. These Figures have been amended to provide sequence identification numbers for nucleotide sequences in excess of nine bases that were, previously, not accompanied by a SEQ ID NO.

Attachments: Replacement Sheets for Figure 17B and Figure 20 (2 pages);
Annotated Drawing Sheets showing changes made to Figure 17B and Figure 20 (2 pages)

Gorenstein *et al.* in view of any one of the following U.S. Patents: 6,514,948 to Raz *et al.*, 6,610,661 to Carson *et al.* or 6,562,798 to Schwartz.

9. Claims 3, 9 and 48-51 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* in view of U.S. Patent 6,229,002 to Janjic *et al.*

Applicants believe the preceding amendments and the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as the rejections set out above.

1. Acronyms In The Claims

The Examiner objected to Applicants' use of the following acronyms in the claims: PSMA, BTLA, TIM-3 and BAFF. Applicants respectfully submit these acronyms are well known in the fields of autoimmunity and cancer research and do not require further definition. However, in order to further Applicants' business interests and without acquiescing to the Examiner's objections, while expressly reserving the right to prosecute the claims as originally filed (or claims similar thereto), Applicants have, for the acronyms cited by the Examiner, amended claim 11 by providing the full name of the target followed by the acronym in parenthesis.

2. Informalities In The Specification

Applicants have amended paragraph **[0028]** to correctly reference Fig. 10B.

3. No New Matter Was Added By The September 17, 2007 Amendment

The Examiner alleges Applicants' September 17, 2007 amendment introduced new matter because U.S. Provisional Patent Application Serial No. 60/523,935 was not incorporated by reference in the application as filed. Applicants respectfully disagree. In the preliminary amendment filed June 14, 2004 Applicants amended the priority claim, as set out in paragraph **[0001],** to include "Ser. No. 60/523,935, Filed November 21, 2003". Applicants note this amended priority claim was filed, *as per* 37 CFR §§1.78(a)(4) and

(a)(5), within four months from the filing date of the instant nonprovisional patent application. On May 12, 2005 Applicants filed another preliminary amendment wherein they deleted, in paragraph **[0001]**, certain benefit claims other than the benefit claim to U.S. Patent Application Serial No. 60/523,935 in the specification as filed. In this May 12, 2005 preliminary amendment, however, Applicants inadvertently omitted reference to U.S. Patent Application Serial No. 60/523,935 in the amended priority claim. Applicants remedied this omission by filing a preliminary amendment on June 09, 2005 wherein they notified the PTO of the inadvertent omission of text and again noted the priority claim to U.S. Patent Application Serial No. 60/523,935. Applicants note that at no time after U.S. Patent Application Serial No. 60/523,935 was properly introduced into the priority claim (*i.e.*, in the preliminary amendment filed June 14, 2004) was reference to U.S. Patent Application Serial No. 60/523,935 expressly deleted in any manner. That is to say, in the preliminary amendment filed June 09, 2005 Applicants merely re-inserted the reference to U.S. Patent Application Serial No. 60/523,935 in the "Related Applications" paragraph on page one of the patent application.

Applicants submit no new matter was added by the September 17, 2007 amendment and that they are free to rely on the teachings in, and derive claims from, the specification of U.S. Patent Application Serial No. 60/523,935 which is rightly part of the priority claim of the instant nonprovisional patent application.

4. Applicants Are Compliant With 37 CFR 1.821–1.825

The Examiner notes that sequence identifiers are not associated with the sequences set out in the following parts of the application as originally filed: i) Table 2, ii) Fig. 17B and iii) Fig. 20. Applicants have amended the specification such that the sequence identification numbers that were associated with the nucleotide sequences at issue in other parts of the specification are, now, also associated with these same nucleotide sequences in excess of nine bases when they appear in the aforementioned table and figures. Because the nucleotide sequences in question had already been assigned sequence identification numbers in sequence listing on file. Therefore, it is not necessary to provide, with the instant response, either: i) a substitute CFR copy of the sequence listing or ii) a substitute paper copy of the sequence listing. Applicants submit

the application is compliant with 37 CFR 1.821–1.825 and request the Examiner withdraw the instant objection.

5. The Claims Satisfy 35 U.S.C. §112, First Paragraph

Claims 7, 8 and 9 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner states that these claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More specifically, the Examiner alleges Applicants have failed to provide a sufficient number of: i) immunostimulatory nucleic acid sequences (other than CpG motifs) and ii) second targets (other than tlr3 and tlr9) that upon binding an aptamer stimulate an immune response to support the genus claim 7. Office Action mailed October 17, 2007, pp. 5-6.

The Examiner is reminded that *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of Section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventors had possession of the subject matter in question. See, In re Edwards, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978) and Fujikawa v. Wattanasin, 39 USPQ 2D 1895, 1904 (Fed. Cir. 1996). With regard to immunostimulatory motifs, Applicants provide a broad teaching of other, non-CpG, immunostimulatory motifs at paragraph **[00167]** of the application as filed. Similarly, at paragraph **[00164]** of the application as filed Applicants describe TLR-9 as part of a ten member family of toll-like receptors that are suitable as a second target wherein the binding of an aptamer to the second target stimulates an immune response.

However, in order to advance business interests and without acquiescing to any argument raised by the Examiner while expressly reserving the right to prosecute the claims as filed, or claims similar thereto, in subsequently filed patent application(s) Applicants have amended claim 7 to include toll-like receptors and claim 3 to include a specific CpG motif. Applicants note the Examiner's rejection of claim 9, under this statutory section, is moot as claim 9 is now withdrawn. Applicants respectfully request

the Examiner withdraw the pending rejection under 35 U.S.C. §112, first paragraph.

6. and 7. The Claims Are Novel

Without acquiescing to any argument raised by the Examiner while expressly reserving the right to prosecute the claims as filed, or claims similar thereto, in subsequently filed patent application(s) Applicants have amended claim 3 (and, thereby, the claims that depend there from) such that, in part, the pending claim recites, "wherein said second sequence is an immunostimulatory CpG motif that stimulates an immune response wherein said CpG motif comprises the formula: rCGyy wherein r is a purine, C is cytosine, G is guanosine and y is a pyrimidine."

It is well settled law that, under 35 U.S.C. § 102, anticipation, "requires that each and every element of the claimed invention be disclosed in the prior art. . . . [i]n addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." Akzo N.V. v. U.S. International Trade Commission, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987). Furthermore, "[t]he Examiner bears the burden of presenting at least a *prima facie* case of anticipation." *In re* Sun, 31 USPQ 2d 1451, 1453. Applicants submit the Examiner has failed to make a *prima facie* case of anticipation. That is to say, none of the art cited by the Examiner discloses each and every element of the invention as claimed.

A. Janjic *et al.* Do Not Anticipate

The Examiner notes the ligand designated 36t (SEQ ID NO: 84) in U.S. Patent No. 6,229,002 ("Janic *et al.*") is identical to ARC124 as described in the instant application. Applicants respectfully submit the Examiner's remarks about the teachings in Janjic *et al.* are of no moment in view of at least the amendments to claims made herein. That is to say, the composition as claimed in claim 3 is chemically distinct from the ligand designated 36t in U.S. Patent 6,229,002. Applicants note it is axiomatic that a chemical compound may be anticipated only if the disclosure, in a single reference, places the compound in question in possession of the public. See, *In re Brown*, 329 F. 2d 1006, 141 U.S.P.Q. 245 (C.C.P.A. 1964). Since U.S. Patent 6,229, is silent on the composition as claimed in claim 3, and the compositions in all the claims that depend there from,

Janjic *et al.* cannot and does not anticipate the claimed embodiments of the present invention.

B. Gorenstein *et al.* Do Not Anticipate

The Examiner alleges the teachings in U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* anticipate the invention as claimed because Gorenstein *et al.* teach,

> a pharmaceutical composition comprising concatenated thioaptamers directed against nuclear growth factors, wherein the *aptamers* also comprise a pathogen-associated molecular pattern antigen such as a CpG molecule[1]. (emphasis added)

Applicants note that the only teaching Gorenstein *et al.* provide about CpG molecules is their use as separate molecules in combination with thioaptamers as an adjuvant. More specifically, Gorenstein *et al.* teach that,

> [w]hen used as a vaccine, that thioaptamer *adjuvant* may also include at least one antigen. In addition to the examples hereinabove, the antigen may be a pathogen-associated molecular pattern antigen, e.g., a CpG molecule, a saccharide, a lectin, a polysaccharide and the like[2]. (emphasis added)

Similarly, Gorenstein et al. teach that.

> [a]nother embodiment of the invention is a vaccine that includes an antigen and a thioaptamer.[3]

Gornstein *et al.*, therefore, are completely silent on a CpG motif which has been incorporated *into the sequence of an aptamer* such that the CpG motif containing aptamer comprises a first sequence capable of binding to a first target and a second sequence capable of binding to a second target wherein said second sequence is an immunostimulatory CpG motif that stimulates an immune response. Because U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* is silent on the composition as claimed in claim 3, Gorenstein *et al.* cannot anticipate the claimed embodiments of the present invention.

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[1] Office Action mailed October 17, 2007, p. 9.

[2] U.S. Patent Publication No. 2004/0265912, paragraph **[0027]**

For the reasons set out above, Applicants submit that neither the Janjic *et al.* or Gorenstein *et al.* can support a rejection under 35 U.S.C. § 102(b) or 35 U.S.C. § 102(e) and, therefore, the rejections raised under these statutory sections must be withdrawn.

8. and 9. The Claims Are Not Obvious

In *KSR International Co. v. Teleflex Inc.*[4] ("KSR"), the Supreme Court reiterated the Graham factors[5] as the basis for determining obviousness. As recently articulated in the "Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103(a) in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*"[6] the Examiner is charged with: i) finding facts concerning the state of the art and the teachings of the references applied and ii) clearly articulating the rationale, based on the facts, in support of the Examiner's rejections under 35 U.S.C. §103(a). Applicants respectfully submit the Examiner fails to meet this burden.

The Examiner alleges that claims 3, 9, 10 and 47 are obvious over U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* in view of any one of the following U.S. Patents: 6,514,948 to Raz *et al.*, 6,610,661 to Carson *et al.* or 6,562,798 to Schwartz. More specifically, the Examiner states that,

> [i]t would have been obvious to one of ordinary skill in the art at the time of the invention to select any known CpG immunostimulatory sequence to use in the inventions of Gorenstein. Absent evidence of some unexpected result, selection of a sequence is simply a matter of choosing between obvious, equivalent alternatives. It is clear form [sic] the art cited above, that SEQ ID NO: 12 was well known in the prior art as a CpG-containing immunostimulatory molecule, and so it would have been obvious to use it, or any other well known CpG molecule in the invention of Gorenstein.[7]

As a threshold observation, Applicants note that Gorenstein *et al.* are silent on a single oligonucleotide, *i.e.* a single aptamer, that has two functionalities – an aptamer

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[3] *Id.* at paragraph **[0026]**.
[4] 127 S.Ct. 1727 (2007).
[5] See, Graham v. Deere, 383 US 1, 17-18 (1966); MPEP 2141.
[6] Federal Register, Vol. 72, No. 195, pp. 57526-57535.
[7] Office Action mailed October 17, 2007, pp. 10-11.

binding domain and an immunostimulatory CpG motif. That is to say, Gorenstein *et al.* are silent on an aptamer comprising a first sequence capable of binding to a first target and a second sequence capable of binding to a second target wherein said second sequence is an immunostimulatory CpG motif that stimulates an immune response. Gorenstein *et al.* only disclose aptamers that bind a single target which, in one embodiment, are "downstream nuclear regulatory factors that *transduce* a intracellular signal from a Toll-like receptor".[8] Thus, Gorenstein *et al.* teach nothing more than a simple aptamer that binds to and modulates the function of a protein, e.g. NF-κB and AP-1 that is involved in mediating an immune response after it has been stimulated.[9] In contrast, the aptamers described by the claimed embodiment of the present invention have a first sequence that binds a, e.g. a protein, *and* a second immunostimulatory sequence that *stimulates* an immune response *independent of* the physiological effect of the binding event between the first sequence and the first target of this same aptamer. Applicants remind the Examiner of the following proposition offered in KSR:

> [i]nventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known.[10]

In this respect the Examiner cites references which only disclose: i) thioaptamers without CpG motifs and ii) CpG molecules without any suggestion for their incorporation into an aptamer, or *vice versa*, so as to create a dual functioning molecule. Applicants, therefore, submit the Examiner only provides, as proscribed by the KSR court, references to building blocks without any rationale of how these building blocks interact to render, as obvious, any of the claimed embodiments of the present invention. Therefore, Applicants respectfully submit the pending claims of the present invention cannot be rendered as obvious by U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* in view of any one of the following U.S. Patents: 6,514,948 to Raz *et al.*, 6,610,661 to Carson *et al.* or 6,562,798 to Schwartz.

The Examiner also alleges that claims 3, 9 and 48-51 are obvious as being

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[8] U.S. Patent Publication No. 2004/0265912, paragraph **[0028]** (emphasis added).
[9] *Id.* at paragraph **[131]**.
[10] 127 S.Ct. 1727, 1741 (2007).

unpatentable over U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* in view of U.S. Patent No. 6,229,002 to Janjic *et al.* In order to support this rejection the Examiner alleges that,

> [i]t would have been obvious to one of ordinary skill in the art at the time of the invention to attach PEG of any molecular weight in the range of 20-45 kDa to the aptamers of Gorenstein in order to obtain improved pharmacokinetic properties as taught by Janjic.

Applicants remind the Examiner that non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom.[11] Applicants, therefore, address their rebuttal of this rejection in view of claim 3 only. Claim 3 does not recite a PEG moiety as an element of the claim. Applicants have already discussed why U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.* cannot sustain the Examiner's pending rejections under 35 U.S.C. § 103. To the extent the Examiner cites U.S. Patent No. 6,229,002 to Janjic *et al.* to render as obvious dependent claims 48-51, which recite the element of a PEG moiety, the Examiner's argument is of no moment for the reasons discussed above. Because U.S. Patent No. 6,229,002 to Janjic *et al.* fails to rehabilitate the primary reference, *i.e.*, U.S. Patent Publication No. 2004/0265912 to Gorenstein *et al.*, that forms the basis for the Examiner's rejection of claim 3, Applicants respectfully submit the Examiner's argument that claims 3, 9 and 48-51 are obvious over Gorenstein *et al.* in view of U.S. Patent No. 6,229,002 to Janjic *et al.* must be withdrawn.

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[11] See, MPEP 2143.03.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit, that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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